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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/938,160	08/23/2001	Clark M. Whitehead	P-191	1257

7590 06/16/2005

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EXAMINER	
KIM, VICKIE Y	

ART UNIT	PAPER NUMBER
1618	

DATE MAILED: 06/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/938,160	WHITEHEAD ET AL.	
	Examiner	Art Unit	
	Vickie Kim	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 31-40* is/are pending in the application.

4a) Of the above claim(s) *31-37 and 40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,38 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/01&11/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. Acknowledgement is made of amendment filed 4/9/2004. Upon entering the amendment, the claims 6-30 are canceled.

2. Claims 1-5 and 31-40 are pending.

3. The claims 1-5, 38 and 39 (elected) are presented for the examination.

4. The claims 31-37 and 40 are withdrawn from consideration as being non-elected. It is noted that there was typographical error found in previous office action(i.e. elected invention of Group I(claims 1-5) and group III(claims 38-39)). The error was made inadvertently where the elected invention should have included group I(claims 1-5) and **group IV**(claims 38-39) instead. However, the said inadvertent error should have been easily recognized and understood as it has corrected.

The examiner's intention was clearly stated in the previous office action where the examiner partially accepted applicant's request for rejoining group IV(claims 38-39) into the elected invention of group I since both group I and IV relates to a method of treating scleroderma whereas group III (claims 31-37 and 40) are directed to a method of inhibiting activated macrophages. If applicant was seriously in doubt, telephonic inquiry should had been made to clarify the confusion. Since the error in question is rather simple and easily understood, the office action issued should be considered to be valid and sustained with correction mentioned hereinabove, and the examination is continued with the elected invention of groups I(1-5) and IV(38-39).

5. Applicant is requested to clarify the status of amendment filed 11/19/03. Although acknowledgement is made of amendment and other papers filed 11/19/03, it is not clear which paper(s) is/are belong to instant application(09/938,160). For instance, Oath (or Declaration, Revocation of power of attorney, A misc. letter(recordation of Merger...), Amendment including specification and remarks and IDS(with 1449,18 pages) are filed on 11/19/03. Since the amendment (both specification and remarks) does not correspond to the instant application(09/938160) and the office action issued by PTO, the examiner is not sure which paper to process. Please clarify the correct status of each paper so that the correct paper(s) can be properly processed into the system.

Response to Arguments

1. Applicant's arguments filed 4/9/04 have been fully considered but they are not persuasive.

2. Rejection under 112

In response to applicant's argument that the term "substantially" is readily understood by the ordinary artisan. Furthermore, the term is defined in the specification at page 9, third paragraph. However, the instant specification fails to define the term "substantially" contrary to what applicant said in the remarks, for instance, the instant specification, at page 9, third paragraph, states "When referring to an "inhibitor [that] does not substantially inhibit COX I or COX II, " we mean that in the ordinary sense of the term." .

There are numerous US patents evidences the uncertainty of the term" substantially" known in the state. For instance, US 2002019342 teaches that the term "substantially" generally means at least about 60% (see paragraph 58) whereas US6730621 teaches the term "substantially" defined as maximum 10%, in some instances as high as 15%(see col. 1, lines 27-32).

The term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not reasonably apprised of the scope of the invention, One of ordinary skill in the art cannot ascertain what degree of inhibition will be classified as "substantial". 20%? 50%? 80%? 99.99%?

Thus, the 112 rejection is maintained as same.

3. Rejection under 103

Applicant's arguments filed 4/9/04 have been fully considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 112, 1st

Scope of enablement

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 and 38-39 are rejected under 35 U.S.C. 112, first paragraph, because

the specification, while being enabling for treating scleroderma comprising administering the specific compounds of the formula as recited in claim 6 such as (Z)-5-fluoro-2-methyl-(4-pyridylidene)-3-(N-bezyl)indenylacetamide or (Z)-5-fluoro-2-methyl-(4-pyridylidene)-3-(N-bezyl)indenylacetamide hydrochloride, does not reasonably provide enablement for the entire scope of "an inhibitor of PDE2 inhibitor wherein said inhibitor does not substantially inhibit COX I or COX II", "an inhibitor of PDE5", "inhibitor of PDE2 and PDE5", "inhibitor has an IC50 for PDE2 of no more than about 25μM and has an IC50 for each of the COX enzymes greater than about 40 μM", "'inhibiting PDE2 in the diseased tissue without substantially inhibiting COX I or COX II" or "a compound of the formula".

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 1 12, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented', (7) the presence or absence of working examples', and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The invention relates to a method of treating scleroderma in a mammal with the administration of the instant compounds.

(2) The state of the prior art

The compounds of the inventions are PDE2 inhibitor; or PDE 2 inhibitor and PDE5 inhibitor.

(3) The relative skill of those in the art

The relative skill of those in the art of pharmaceuticals is high.

(4) The predictability or unpredictability of the art

The unpredictability of the pharmaceutical art is very high.

In fact, the courts have made a distinction between mechanical elements function the same in different circumstances, yielding predictable results, chemical and biological compounds often react unpredictably under different circumstances. Nationwide Chem. Com. v. Wright, 458 F. supp. 828, 839, 192 USPQ 95, 105(M.D. Fla. 1976); Aff'd 584 F.2d 714, 200 USPQ 257 (5th Cir 1978); In re fischer, 427 F.2d 833 839, 166 USPQ 10, 24(CCPA 1970). Thus, the physiological activity of a chemical or biological compound is considered to be an unpredictable art. For example, in Ex Parte Sudilovsky the Court held that Appellant's invention directed to a method for preventing or treating a disease known as tardive dyskinesia using an angiotensin converting enzyme inhibitor involved unpredictable art because it concerned the pharmaceutical activity of the compound. 21 USPQ2II 1702, 1704-5(BDAI 1991)4 In re Fisher, 427 F.2d 1557, 1562, 29 USPQ, 22 (holding that the physiological activity of compositions of adrenocorticotropic hormones was unpredictable art; In re Wright, 9999 F.2d 1577, 1562, 29 USPQ d, 1570, 1513-14 (Fed. Cir. 1993) (holding that the physiological activity of RNA viruses was unpredictable art); Ex Parte Hitzeman, 9 USPQZd 1821, 1823 (BDAI 1987); Ex Parte

Singh, 1 7 USPQZII 1714, 1715, 1716 (BPAI 1990). Likewise, the physiological or pharmaceutical activity of treating multiple sclerosis prior to filling of the instant invention was an unpredictable art.

(5) The breadth of the claims

The claims are very broad due to the vast number of possible compounds represented the formula (formula 1) or of that are described as being PDE2 inhibitor and/or PDE5 inhibitor wherein said PDE2 inhibitor does not "substantially inhibitor COXI or COX II" or has "an IC50 for PDE2 of no more than about 25μM and has an 1C50 for each of the COX enzymes greater than about 40μM".

(6) The amount of direction or guidance presented

The instant specification discloses that compounds employed in this invention are useful inhibitors of PDE2 and/or PDE5 inhibitor, most preferably compounds of no more than about 25μM (page 8, lines 1-10). The specification discloses compounds of the formula I and other compounds disclosed in US 5,401,77, 606,818, 5998,477 and 5,965,619 as compounds that are potentially suitable for the instant invention (page 5, line 2 1 thru page 7, line 26 and page 10, lines 5-9). As the specific embodiment of the invention, the specification discloses the compound of Example 1 or Example 38 that has been evaluated for the inhibitory effects on cyclooxygenase (COX) and/or phosphodiesterase activity by known assay methods (method taught in US 09/046,739 and method using radioactive 311 cyclic GMP described in (Thomson et a1., Advances in Cyclic Nucleotide Research, 10:69-92, 1979) and tested for inducing apoptosis in U937 cell lines (pages 44-510f the specification, Biological Effects A, B and C).

However, the specification provides insufficient guidance or direction, in the way of enablement for the full scope of (i) PDE2 inhibitor and/or PDE5 inhibitor, PDE2 inhibitor without "substantially inhibit COX I or COX II" or PDE2 inhibitor having "an IC50 for PDE2 of no more than about 25μM and has an IC50 for each of the COX enzymes greater than about 40 μM" and (ii) the claimed scleroderma treatment in humans or mammals with said compounds of the formula I or compounds that are potentially suitable for the instant invention. As stated above, the instantly claimed PDE2 inhibitor and/or PDE5 inhibitor read on numerous possible compounds that are capable of having "no more than about 25μM and has an IC50 for each of the COX enzymes greater than about 40 μM" or without substantially inhibit COX I or COX II, " necessitating an exhaustive search for the embodiments suitable to practice the claimed invention. The specification fail to provide adequate representation for one having ordinary skill in the art to ascertain which compounds of PDE2 inhibitor would fall within the claimed PDE2 " does not substantially inhibit COX I or COX II" or have " an IC50 for PDE2 of no more than about 25μM and has an IC50 for each of the COX enzymes greater than about 40μM" and would be capable of accomplishing the desired result of the claimed invention without undue amount of experimentation. The specification fails to provide sufficient information or guidance that all compounds that are potentially suitable for the invention work similarly as to compound of the Example 1 or Example 38. In addition, the specification does not provide adequate representation regarding the conclusion of the claimed utility in scleroderma treatment from the exemplified apoptosis induction of U937 cells by compound 38. No evidence that the apoptosis

induction of U937 cells by compound 38 is effective in the claimed scleroderma treatment in human or mammals is provided. Scleroderma is an inflammatory demyelinating disease of the central nervous system that involves diverse pathophysiological mechanisms. The cause of MS is tmknown and the pathogenesis of scleroderma is unclear. At the time of the invention was made it was not known that apoptosis is a definite cause of scleroderma and the inhibition of apoptosis leads to the definite treatment of scleroderma (see "Cell Death; For Better of For Worse in MS", NMSS Research Highlights, Winter/spring 2001). The lack of significant guidance from the specification or prior art with regard to treat scleroderma in human or mammals with the administration of the instant compounds makes the claimed invention unpredictable, and makes the practitioner to turn to trial and error experimentation to practice the instant compounds for the claimed utility.

(7) The presence or absence of working examples

As stated above, the specification discloses the compound of Example 1 or Example 38 having "low COX inhibition" and/or "an IC50 for PDE2 of no more than about 25μM and has an IC50 for each of the COX enzymes greater than about 40μM" that is useful for inducing apoptosis in U937 cell lines.

(8) The quantity of experimentation necessary

As stated above, when the above factors are weighed, it would take undue trials And errors to practice the claimed invention. Therefore, undue experimentation becomes the burden of the practitioner.

*** If applicant traverses the rejection above, it would be the admission on the record that all PDE 2 inhibitors(that has substantially no inhibition of COX I or COX II) has same therapeutic effectiveness against scleroderma.

Claim Rejections - 35 USC § 112,2nd

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5 and 38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. The term "substantially" in claim 1 is a relative term which renders the claim indefinite. The term " substantially " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section

351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. Claims 1-5 and 38-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Kauffman et al(US 5,270,047).

Claims are drawn to a method of treating scleroderma using an effective amount of PDE2 inhibitor that does not substantially inhibit COX I or COX II.

Kauffman et al(US'047) teaches a dipyridamole and its use in the scleroderma(proliferative disease), see abstract.

Since dipyridamole inherently inhibits PDE 2 activity and does not substantially inhibit COXI or COX II(as evidenced by numerous documents* available in the art at the time the invention was filed), all the critical elements required by instant claims are well taught by the cited reference and the claims are not patentably distinct over the prior art of the record.

(*) Dipyridamole's inherent features (i.e. inhibition of PDE 2 activity or no COX activity inhibition) is well supported by extrinsic documents available in the state of the art(see PTO-892).

(i) Fisher(US5922595), at see col. 11 lines 8-9, teaches that dipyridamole is a inhibitor of PDE 2)

(ii)Weinstein et al(US 6569638) teaches that dipyridamole inhibits PDE2 and PDE5 activity, see column 7, lines 1-26.

(iii) Lugnier(1992, abstract only) teaches dipyridamole as a potent PDE 2 inhibitor.

(iii) Greenwald(1979, abstract only) teaches that dipyridamole does not inhibit COX, see abstract.

The claimed subject matter(i.e. a method of treating scleroderma using a PDE 2 inhibitor) is clearly anticipated because the scope of claims are well embraced by the teaching cited reference because the patent clearly teaches the medical utility of dipyridamole, (inherently a PDE2 inhibitor that does not inhibit COX I or II) in the treatment of scleroderma) as set forth immediately above, and is not considered to be patentably distinct over the prior art of the record.

Thus, the claims are properly included in this rejection.

Claim Rejections - 35 USC § 103

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. Claims 1-5 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sperl et al(US 6,066,634) in view of Hersh (US 5,827,886).

Sperl et al(US'634, hereinafter) teach N-benzyl-3-indenylacetamides(compound 38, see specification at pages 41 and 47), see abstract and patented claims 1 and 28 in particular. US'634 also teaches that the said compounds are known PDE inhibitors and that they do not substantially inhibit COX I and COX II, see col. 28, line 49-col.29, line 9. US'634 also teaches the employment of its compounds in a method of treating autoimmune diseases such as rheumatoid arthritis, see col. 5, lines 17-18.

Since applicant teaches compound 38 as a preferred PDE 2 inhibitor (because it has been selected to represent other PDE2 inhibitors for showing its effectiveness in the instant specification, see pages 46-49) , although Sperl states no PDE2 inhibition by compound 38(regardless of that Sperl's statement is true or not because it is the inherent feature), the therapeutic effectiveness of PDE2 inhibitor(e.g.compound 38) against autoimmune diseases is well proven.

US'634 does not particularly teach scleroderma as an autoimmune disease.

However, Hersh teaches that scleroderma is an autoimmune disease such as scleroderma or rheumatoid arthritis and further teaches that both scleroderma and rheumatoid arthritis can be benefited by same drug treatment because they share similar pathogenesis, see column 6, lines 35-40. Thereofore, It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ compound 38 in a method of treating scleroderma when Spearl et al is taken in view of Hersh, see Hersh (US'886) at col.1, lines 47-48.

One of ordinary skill in the art would have been motivated to employ compound 38 in a method of treating scleroderma because compound 38 is known to be useful in methods of treating autoimmune diseases, a class of diseases which includes scleroderma.

It is noted that the newly added limitations in preamble does not have patentably weight because the compound38 has been taught in the primary reference, therefore, it is inherently met and does not render the claims patentably distinct over the prior art of the record.

Conclusion

1. No claim is allowed. This is 2nd non-final rejection.

2. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vickie Kim whose telephone number is 571-272-0579. The examiner can normally be reached on Tuesday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Chris Low be reached on 571-272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

VICKIE KIM
PRIMARY EXAMINER

Vickie Kim
June 12, 2005
Art unit 1618